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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/576,492	02/06/2007	Gordon Bruton	PB60543USw	3822

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EXAMINER

COLEMAN, BRENDA LIBBY

ART UNIT	PAPER NUMBER
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1624

NOTIFICATION DATE	DELIVERY MODE
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11/30/2009

ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No. 10/576,492	Applicant(s) BRUTON ET AL.	
	Examiner Brenda L. Coleman	Art Unit 1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 10-12 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 10-12 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____. |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>4/18/06</u> . | 6) <input type="checkbox"/> Other: ____. |

DETAILED ACTION

Claims 9-12 are pending in the application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 9-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for pharmaceutically acceptable salt forms, does not reasonably provide enablement for solvates. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. The claim is drawn to solvates. But the numerous examples presented all failed to produce a solvate. These cannot be simply willed into existence. As was stated in *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190 “The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there is no evidence that such compounds exist... the examples of the '881 patent do not produce the postulated compounds... there is ... no evidence that such compounds even exist.” The same circumstance appears to be true here: there is no evidence that solvates of these compounds actually exist; if they did, they would have formed. Hence, applicants must show that solvates can be made, or limit the claims accordingly.

Art Unit: 1624

2. Claim 12 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The scope of the method claims is not adequately enabled solely based on histamine H3 receptor activity provided in the specification.

In evaluating the enablement question, several factors are to be considered. In *re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988); *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

The nature of the instant invention has claims, which embrace substituted diazepam compounds.

HOW TO USE: Claim 12 is to a method for treating any and all neurological diseases associated histamine H3 receptor activity. Any evidence presented must be commensurate in scope with the claims and must clearly demonstrate the effectiveness of the claimed compounds. The scope of claim 12 includes diseases and/or conditions not even known at this time, which may be associated with histamine H3 receptor activity. While the treatment of allergic rhinitis have been linked with histamine H3 receptor activity the art does not recognize use of such inhibitors as broad based drugs for treating all disorders instantly embraced. It is difficult to treat many of the disorders

Art Unit: 1624

claimed herein.

The scope of "neurological disease" cannot be deemed enabled. The term "neurological disease" covers a broad array of different disorders that have different modes of action and different origins. The term covers such diverse disorders as Alzheimer's Disease; Parkinson's Disease; ALS and variants such as forms of ALS-PDC; Gerstmann-Straussler-Scheinker Disease (GSS); Pick's Disease; Diffuse Lewy Body Disease; Hallervorden-Spatz disease; progressive familial myoclonic epilepsy; Corticodentatonigral degeneration; progressive supranuclear palsy (Steele-Richardson-Olszewski); Huntington's disease; more than a dozen dementias collectively called "frontotemporal dementia and Parkinsonism linked to chromosome 17" (FTDP-17); Tourette's syndrome; Shy-Drager syndrome; Friedrich's ataxia and other spinocerebellar degenerations; Olivopontocerebellar atrophy (OPCA); spasmodic torticollis; Striatonigral degeneration; various types of torsion dystonia; certain spinal muscular atrophies, such as Werdnig-Hoffmann and Wohlfart-Kugelberg-Welander; Hereditary spastic paraplegia, Primary lateral sclerosis; peroneal muscular atrophy (Charcot-Marie-Tooth); Creutzfeldt-Jakob Disease (CJD); Hypertrophic interstitial polyneuropathy (Dejerine-Sottas); retinitis pigmentosa; Leber's Disease; and Hypertrophic interstitial polyneuropathy. These exhibit a very broad range of effects and origins. For example, some give progressive dementia without other prominent neurological signs, such as Alzheimer's disease, whereas other dementias have such signs, such as Diffuse Lewy Body Disease. Some give muscular wasting without sensory changes, e.g. ALS, and some do have the sensory changes such as Werdnig-

Art Unit: 1624

Hoffmann. Some are abnormalities of posture, movement or speech, such as Striatonigral degeneration, and other are progressive ataxias, such as OPCA. Some are linked to tau mutations, such as Alzheimer's disease and FTDP-17, and other such as Parkinson's clearly do not. Some affect only vision such as retinitis pigmentosa. Even within those that fall into the same category of effects, there are often striking differences. For example, Alzheimer's disease and Pick's disease both give progressive dementia without other prominent neurological signs. But the characteristic Alzheimer's neurofibrillary tangles are not seen in Pick's Disease, which has straight fibrils, as opposed to the paired helical filaments of Alzheimer's disease. Pick's Disease gives lobal atrophy, not seen in Alzheimer's disease. There are differences in origins, even with what little is known. Thus, among progressive dementias, CJD is definitely caused by an infectious agent; so far as can be determined, this is not so for Huntington's disease. Even among the hereditary disorders, the origins are different. Thus, FTDP-17 comes from chromosome 17, Huntington's disease from 4, and the neurodegenerative disorder that people with Down's syndrome develop later in life is presumably connected in some way to 21.

The great majority of these have no treatment at all, and of those that do, none or virtually none have been treated with such inhibitors as are disclosed here. The great diversity of diseases falling within the "neurological disease" category means that it is contrary to medical understanding that any agent (let alone a genus of trillions of compounds) could be generally effective against such diseases. The intractability of these disorders is clear evidence that the skill level in this art is low relative to the

Art Unit: 1624

difficulty of the task. Further, what little success there has been does not point in this direction. Thus, what very few treatments that the massive research effort on Alzheimer's disease has produced are means of providing Acetylcholinesterase inhibition, unrelated to the mechanism of action in this case.

No screening protocol(s) are ever described. Thus, no evidence of in vitro effectiveness is seen in the specification for one of the instantly claimed substituted diazepam compounds. In general, pharmacological activity is a very unpredictable area. In cases involving physiological activity "the scope of the enablement obviously varies inversely with the degree of unpredictability of the factors involved." In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970). Since this case involves unpredictable in vivo physiological activities, the scope of the enablement given in the disclosure presented here was found to be low.

Where the utility is unusual or difficult to treat or speculative, the examiner has authority to require evidence that tests relied upon are reasonably predictive of in vivo efficacy by those skilled in the art. See In re Ruskin, 148 USPQ 221; Ex parte Jovanovics, 211 USPQ 907; MPEP 2164.05(a).

Patent Protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. Tossing out the mere germ of an idea does not constitute enabling disclosure. Genentech Inc. v. Novo Nordisk 42 USPQ2d 1001.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claim 10 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

- a. Claim 10 is vague and indefinite in that it is not known what is meant by the nomenclature of the 7th species which is missing an open parenthesis.
- b. Claim 10 is vague and indefinite in that it is not known what is meant by the second occurrence of the species 1-cyclobutyl-4-({3-[(3-pyridinylmethyl)oxy]phenyl}carbonyl)hexahydro-1H-1,4-diazepine (species 45) which is a duplicate of the 44th species.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

4. Claims 10-12 are rejected under 35 U.S.C. 102(e) as being anticipated by Martin et al., U.S. Patent No. 7,449,464. Martin teaches the compounds, compositions and method of use of the compounds of formula (I) where R³ is phthalazin-1-one; X is CH₂; R² is H or F; and R¹ is n-butyl, -CH₂CH(CH₃)CH₂CH₃, -CH₂CH(CH₂CH₃)CH₂CH₃, n-

Art Unit: 1624

pentyl, propyl, cyclopropylmethyl, $-\text{CH}_2\text{C}(\text{CH}_3)_3$, $-\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)_2$, isopropyl, $-\text{CH}_2\text{CH}(\text{CH}_3)_2$, etc. as set forth in column 110, 111, 114, 116 and 119.

5. Claims 10-12 are rejected under 35 U.S.C. 102(e) as being anticipated by Ratcliffe et al., U.S. Patent No. 7,148,215. Ratcliffe teaches the compounds, compositions and method of use of the compounds of formula (I) where R^3 is 7-chloro-6-methyl-8-amido-3,4-dihydro-1-pyrrolo[1,2-a]pyrazine, 7-cyano-6-methyl-8-amido-3,4-dihydro-1-pyrrolo[1,2-a]pyrazine, 7-chloro-6-trifluoromethyl-8-amido-3,4-dihydro-1-pyrrolo[1,2-a]pyrazine, 7-cyano-6-trifluoromethyl-8-amido-3,4-dihydro-1-pyrrolo[1,2-a]pyrazine, 7-chloro-8-amido-3,4-dihydro-1-pyrrolo[1,2-a]pyrazine, 7-cyano-8-amido-3,4-dihydro-1-pyrrolo[1,2-a]pyrazine, etc.; X is NHCO ; R^2 is H; and R^1 is isopropyl as set forth in column 37, 43 and 126.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brenda L. Coleman whose telephone number is 571-272-0665. The examiner can normally be reached on 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.

Art Unit: 1624

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/Brenda L. Coleman/
Primary Examiner, Art Unit 1624